M E M O R A N D U M

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To: General and Plastic Surgery Devices Panel Members

From: David Krause, Ph.D.

Subject: Proposal to Reclassify the Absorbable Hemostatic Agent Device

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Regulatory History of Absorbable Hemostatic Agents and Dressings:

Originally, the absorbable hemostatic agents and dressings were regulated as drugs and required a New Drug Application (NDA) for marketing approval. At the time of the Medical Device Amendments of 1976 (the 1976 Amendments) to the Food, Drug and Cosmetic Act (the Act) (21 USC 360C), a number of products regulated as drugs were transferred to device regulations since these were more appropriate. One of these "transitional" devices was the absorbable hemostatic agent and dressing. Transitional products were automatically classified as Class III medical devices.

The 1976 Amendments as amended by the Safe Medical Device Act (SMDA) of 1990 and the FDA Modernization Act (FDAMA) of 1997 provide regulations for the reclassification and regulation of medical devices intended for human use. FDA may elect to reclassify a medical device, including the Class III medical devices into a lower regulatory class that can reasonably assure their safety and effectiveness for their intended use.

The Act established three categories (classes) of medical devices depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three classes are Class I (general controls), Class II (special controls), and Class III (pre-market approval). General controls are sufficient to provide reasonable assurance of the safety and effectiveness of Class I devices. General controls include the following: prohibition against adulterated or misbranded devices, premarket notification (510(k)), banned devices, the quality system regulation that includes design controls and good manufacturing processes (GMPs), registration of manufacturing facilities, listing of device types, record keeping, etc.

Class II devices are those that cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of such devices. These devices are regulated using special controls and general controls. Special controls include guidelines (guidance documents), performance standards, postmarket surveillance, clinical data, labeling, tracking requirements, and other appropriate actions the

Secretary of the Department of Health and Human Services deems necessary to provide such assurance.

Class III devices are those for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness. These devices are life sustaining, life supporting, or substantially important in preventing impairment of human health, or they present unreasonable risk of illness or injury. Class III devices are regulated by using "valid scientific evidence" to establish the safety and effectiveness of the device. Valid scientific evidence includes well-controlled investigations, partially-controlled studies, uncontrolled studies, well-documented case histories, and reports of significant human experience.

When most devices were classified in the late 1970s and early 1980s, most Class I and Class II devices were cleared for marketing via the 510(k) process. Some Class I devices were also exempted from 510(k) clearance. Now many Class I devices and a few Class II devices are exempt from 510(k) clearance because their safety and effectiveness can be reasonably assured by other general controls, particularly by the quality system regulation general control.

The absorbable hemostatic agents and dressings approved via the PMA or NDA regulatory process to date contain porcine or bovine gelatin, bovine collagen, or regenerated oxidized cellulose. The two most recently approved absorbable hemostatic agents and dressings, FloSeal and CoStasis, additionally contain bovine thrombin and therefore are combination products, i.e., products containing both a device and biological component.

FDA has regulated absorbable hemostatic agents under regulation number 21 CFR §878.4490, Absorbable Hemostatic Agent and Dressing. These products are defined as "a device intended to produce hemostasis by accelerating the clotting process of blood. It is absorbable. As of May 28, 1976, it has required an approval under section 515 of the act to allow commercial distribution of an absorbable hemostatic agent."

Since 1976, CDRH has approved ten absorbable hemostatic agent and dressing PMAs. A number of hemostatic agents were approved through the new drug process and then transferred to CDRH for regulation after 1976. Most of these products should be familiar to you. Table 1 identifies products included in the absorbable hemostatic agent and dressing group.

Table 1

Absorbable Hemostatic Agents Approved Through PMA or NDA

Product	Present Application Holder	Application Number**	Characteristics	Approval Date
Gelfoam	Pharmacia and Upjohn	N18286	Porcine Gelatin molded into a sponge	Available 1945 July 8, 1983
Oxycel*	Becton Dickinson	N5798	Sponge made of Oxidized Cellulose	September 12, 1945
Surgicel	Ethicon	N12159	Sponge made of Regenerated Oxidized Cellulose	October 14, 1960
Avitene	Davol	N17600 and P800002	Bovine Collagen	August 26, 1976 October 24, 1980
Collastat	Integra LifeSciences	P810006	Bovine Collagen	December 10, 1981
Superstat*	Superstat	P810040	Bovine Collagen	January 29, 1982
Instat	Ethicon	P830079	Bovine Collagen	October 10, 1985
Helistat Helitene	Integra LifeSciences	P850010	Bovine Collagen	November 8, 1985
Hemopad Novacol	Datascope	P850023	Bovine Collagen	May 27, 1986
Actifoam*	Coletica	P930030	Bovine Collagen	August 15, 1995
Surgifoam Spongistan	Ethicon	P990004	Porcine Gelatin sponge	September 30, 1999
FloSeal Hemostat	Baxter Healthcare	P990009	Flowable Bovine Gelatin Matrix and Licensed Bovine Thrombin	December 8, 1999
CoStasis	Cohesion Technologies	P990030	Flowable Bovine Collagen and Licensed Bovine Thrombin combined with Autologous Platelets	June 13, 2000

* Not sold in the US at this time.

** Applications Numbers starting with "N" indicate products approved in the Center for Drugs and Numbers starting with "P" are products approved in the Center for Devices.

Risks to Health

FDA regulates many other medical devices manufactured from similar animal source materials as Class III, Class II, and unclassified devices. For example, the femoral artery sealing device,

which may have a porcine or bovine collagen or gelatin component, is regulated as a Class III medical device. Collagen surgical mesh, gelatin coated surgical mesh, collagen suture, collagen dura replacement, and other collagen/gelatin-containing implants are regulated as Class II medical devices. Other collagen/gelatin-containing medical devices, such as the porcine wound dressings, are currently regulated as unclassified medical devices.

In order to summarize the potential risks associated with the use of the absorbable hemostatic agents and dressings, we reviewed the adverse event reports submitted to the agency via the Medical Device Reporting (MDR) System which was voluntary from 1992 until 1996 when it became mandatory for manufacturers to report any device failures they were aware of. The MDRs for the absorbable hemostatic agents and dressings received by the Agency are summarized in Table 2.

Table 2: Adverse Events Reported

Adverse Event	Absorbable Hemostatic Agents without Thrombin	Absorbable Hemostatic Agents with Thrombin	Total Events
Sinus Infection	1	5	6
Paralysis following off-label placement in vertebral column	5	0	5
Infection following tooth extraction	5	0	5
Product deployment failure	0	5	5
Granuloma	2	0	2
Abscess	2	0	2
Product failure (continued bleeding observed)	0	2	2
Abdominal Infection	1	1	2
Bowel Obstruction	1	0	1
Hematoma	1	0	1
Foreign Body Reaction	1	0	1
Intermittent ischemia	0	1	1
Stroke	0	1	1
Seroma	0	1	1
Tissue Necrosis	1	0	1
Couldn't figure out how to store	1	0	1
Interference with wound healing	0	1	1
Total	21	17	38

The following literature articles are indicative of the published literature on absorbable hemostatic agents and dressings. These articles discuss absorbable hemostatic agents and dressings and also describe some potential risks of using these devices. Copies of these articles are provided in Tab 2c.

1. Arand AG and Sawaya R. Intraoperative chemical hemostasis in neurosurgery. Neurosurgery 18(2): 223-33 (1986).

2. Bloom AL and Thomas DP. Eds. "*Haemostasis and Thrombosis*" Churchill Livingstone (London, England, 1987) pp. 614-5.

3. Browder IW and Litwin MS. Use of absorbable collagen for hemostasis in general surgical patients. Am. Surg. 52(9): 492-4 (1986).

4. DeLustro F, Dasch J, Keefe J and Ellingsworth L. Immune responses to allogenic and xenogeneic implants of collagen and collagen derivatives. Clin. Orthop. 260: 263-79 (1990).

5. Evans BE. Local hemostatic agents. NY State Dent. J. 47(4): 109-14 (1977).

6. Light RE. Hemostasis in Neurosurgery. J. Neurosurgery 2(5): 414-34 (1945).

7. Light RE and Prentice HZ. Surgical investigation of a new absorbable sponge derived from gelatin for use in hemostasis. J. Neurosurgery 2(5): 435-55 (1945).

8. Lindstrom PA. Complications from the use of absorbable hemostatic sponges. AMA Arch. Surg. 73: 133-41 (1956).

9. Schwartz SI. Ed. "*Principles of Surgery, 7th Edition*" McGraw-Hill (New York, 1999) pp. 92-93.

These articles, as well as others, and absorbable hemostatic agent and dressing product labels were reviewed in order to compile the risks identified in Table 3. Tables 3 also identifies the methods that will be proposed to ameliorate these risks.

Table 3: Table of Potential Risks and Controls

Potential Risk	Control
Uncontrolled bleeding due to device failure	Animal Studies and/or Clinical Data
Hematoma as a result of continued bleeding following device application	Animal Studies and Product Labeling
Potentiation of bacterial growth leading to increased infections and Fever	Animal Studies and Product Labeling
Wound dehiscence due to device interposition at the wound edge	Product Labeling
Inflammation and/or edema due to foreign body reaction	Product Labeling
Adhesion formation	Animal Studies
Failure to be absorbed	Bench Testing and Animal Studies
Reduced strength of methylmethacrylate adhesion when used to attach prosthetic devices to bone surfaces	Product Labeling
Aspiration into transfusion filters may activate coagulation *in vitro*	Bench Studies and Product Labeling
Use of antiplatelet drug therapy, systemic heparinization and cardiopulmonary bypass may increase risk for hemostatic agent failure	Product Labeling
Use of the hemostatic agent in closed spaces may result in pressure causing nerve damage or tissue necrosis	Product Labeling
Accidental injection into the intravascular space may result in embolization	Product Labeling
Paralysis due to swelling of the product and exertion of pressure onto nerves	Product Labeling

Table 4 lists the additional risks for absorbable hemostatic agents and dressings that contain bovine thrombin.

Table 4: Table of Additional Potential Risks for Products with Thrombin

Potential Risk
Allergic reaction (antibodies to collagen, gelatin, thrombin) and potential antibody cross reaction (bovine Factor Va antibodies may cross react with human Factor Va resulting in coagulopathy
Inability to assemble or deploy the device, mechanical failure of the device and device malfunction such as clogging

Proposed Reclassification:

The Agency is proposing that the absorbable hemostatic agents and dressings that do not contain bovine thrombin may be reclassified to a lower classification (Class II, special controls). These devices have been regulated by CDRH since 1976, and previous to that were regulated as drugs since the 1940s when both Gelfoam and Oxycel were introduced into the marketplace. During this time a great deal of clinical and preclinical data has been collected that indicate that these devices are safe and effective in controlling bleeding when used in accordance with their approved labeling. The data reported in the literature and medical device reporting have identified the greatest potential risks to the patients. These are identified in Table 2. The Agency feels that all of these potential risks can be addressed via special controls in the form of a guidance document. The applications affected by this reclassification would include all of those listed in Table 1 except those that contain bovine thrombin. The products within this category are currently manufactured from the following materials:

Absorbable Gelatin Sponge: The gelatin sponge is an absorbable material created from porcine gelatin through which nitrogen has been bubbled in order to produce a porous product. This method was first introduced by Correll and Wise in 1945. The sponge has no intrinsic hemostatic action but induces hemostasis through its intensely porous structure, which enables it to absorb 45 times its weight in blood. As it fills with blood the platelets come into close contact and begin to collide initiating the clotting cascade.

Oxidized Cellulose: Oxidized cellulose is a fabric material that is obtained by the oxidation of cotton, gauze, or other cellulose fabric using nitrous oxide to achieve oxidation. The process was first described by Yackel and Kenyon of Eastman Kodak Laboratories in 1942. This reaction converts certain of the hydroxyl radicals to carboxyl groups and makes the material soluble at physiological conditions. The low pH of the cellulosic acid within the product has caustic properties that lead to hemostasis via the initial denaturation of blood proteins.

Regenerated Oxidized Cellulose: Similar to oxidized cellulose, but cellulose is first dissolved and then extruded as a continuous fiber. The fabric made from the fiber is very uniform in chemical composition and its oxidation is more closely regulated. This uniform oxidation results in less variation in absorbability of the material. The regenerated oxidized cellulose induces hemostasis in a manner identical to oxidized cellulose.

Microfibrillar Collagen: Microfibrillar collagen is a water-insoluble, partial hydrochloric acid amino salt of natural collagen in the form of fibers containing microcrystals prepared from purified bovine dermal collagen. Microfibrillar collagen acts primarily by reaction with platelets. Platelets attach to specific sites on collagen and degranulate initiating the hemostatic cascade leading to a fibrin clot.

Continued Class III Status for Absorbable Hemostatic Agents and Dressings containing Bovine Thrombin:

While the Agency feels that the absorbable hemostatic agents and dressings and the associated risks are well understood for those that do not include bovine thrombin, this cannot be said for

hemostatic agents that include bovine thrombin. A number of recent publications have drawn attention to safety concerns for bovine thrombin, in particular antigenic reactivity in humans. These concerns may not be adequately addressed by special controls and therefore, those hemostatic agents, which include bovine thrombin, should remain Class III and continue to require a PMA for marketing.

Proposed Identification for Absorbable Hemostatic Agent and Dressing for the Code of Federal Regulations:

PRESENT CFR LISTING for ABSORBABLE HEMOSTATIC AGENT and DRESSING

(a) *Identification.* An absorbable hemostatic agent or dressing is a device intended to produce hemostasis by accelerating the clotting process of blood. It is absorbable
(b) *Classification.* Class III.
(c) *Date PMA or notice of completion of a PDP is required.* As of May 28, 1976, an approval under section 515 of the act is required before this device may be commercially distributed. See § 878.3.

PROPOSED IDENTIFICATION for THE ABSORBABLE HEMOSTATIC AGENT and DRESSING

(a) *Identification.* An absorbable hemostatic agent or dressing is a device intended to produce hemostasis by accelerating the clotting process of blood. It is absorbable.
(b) *Classification.* Class II for those without bovine thrombin. Class III for those containing bovine thrombin.
(c) *Date PMA or notice of completion of a PDP is required.* As of May 28, 1976, an approval under section 515 of the act is required before this device may be commercially distributed. See § 878.3.

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